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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/087,411 | 03/01/2002 | Gary P. Schroth | 9584-030-999 | 6226 |

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| EXAMINER |
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SITTON, JEHANNE SOUAYA

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| ART UNIT | PAPER NUMBER |
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1634

DATE MAILED: 08/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

**Advisory Action
Before the Filing of an Appeal Brief**

Application No.

10/087,411

Applicant(s)

SCHROTH, GARY P.

Examiner

Jehanne S. Sitton

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--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 31 July 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on 31 July 2006. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because

(a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ They raise the issue of new matter (see NOTE below);

(c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☐ Applicant's reply has overcome the following rejection(s): _____.

6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☐ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____.

Claim(s) objected to: _____.

Claim(s) rejected: _____.

Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attachment.

12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____

13. ☐ Other: _____.

Attachment

1. The response traverses the rejection. The response asserts that as stated in their previous response dated December 21, 2005, applicant's disagree that the ordinary artisan would be motivated to optimize specificity in the DBL-IBL nucleic acid pairs of Chee with the orthogonal nucleobases as taught by Collins because one of skill in the art might arrive at probes that are too specific. The response further asserts that "Chee et al provides an example where highly specific probes would not be helpful. In one embodiment, probes 'that bind in a sequence dependent but not highly sequence specific manner' are used to decode cloned nucleic acids" and cites para 0122. This argument has been thoroughly reviewed but was found unpersuasive. Chee teaches that each probe should hybridize to its corresponding decoder probe. Thus, it is clear that the specificity should be achieved such that each probe is specific for its corresponding decoder probe, and that non specific hybridization should be avoided. Further, Chee specifically teaches the parameters for specificity at paragraph 0069, stating that the IBL-DBL pairs should "allow both a) dissociation, if necessary; and b) efficient hybridization", and teaches dissociation constants at para 0065. Also, Collins teaches how the orthogonal nucleobases affect specificity (Examples 1 and 2). Therefore, given the teachings of Chee and Collins, the knowledge required to achieve appropriate specificity was provided by the prior art. Although Chee exemplifies specificity with the use of probe length, the state of the art at the time the invention was made taught that specificity optimization included a number of different factors, including the use of orthogonal nucleobases, which Chee suggests to use in the context of nucleic acids. Therefore, not only does Chee suggest the use of orthogonal nucleobases in the context of nucleic acids and teaches that DBL-IBL probes can be made up of nucleic acids, but Collins provides ample

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motivation and a reasonable expectation of success for the use of orthogonal nucleobases in nucleic acid hybridization to minimize non specific hybridization and non specific binding, increase accuracy of detection in nucleic acid hybridization assays, and allow more precise control over hybridization through the use of an expanded “alphabet” of bases. The use of orthogonal nucleobases to reduce non specific hybridization between nucleic acid molecules was known in the art at the time the invention was made and is an obvious variation in methods requiring the manipulation of nucleic acid hybridization specificity. Collins specifically teaches that the use of orthogonal nucleobases to increase accuracy of detection (col. 2, lines 40-53) and reduce non specific hybridization (para bridging cols 14 and 15).

The response further asserts that elsewhere, Chee teaches IBL-DBL pairs where optimization of specificity can be achieved by altering probe length. The response asserts that achieving higher specificity is not synonymous to optimizing specificity in Chee et al because the specificity of the system in Chee appears already optimized without the need for modifications. These arguments have been thoroughly reviewed but were found unpersuasive. Although with regard to specificity, Chee teaches optimization with length of IBL-DBL probes (para 0069), as noted in the MPEP, chapter 2123, “Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or non preferred embodiments. In re Susi, 440 F.2d, 169 USPQ 423 (CCPA 1971)”. At the time the invention was made, a number of different ways were known in the prior art to optimize hybridization specificity between nucleic acids, including length of nucleic acid probes, GC content, salt concentration, temperature, and as exemplified by Collins, the use of orthogonal nucleobases. Collins specifically teaches that orthogonal nucleobases such as iso-C and iso-G can be used to

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minimize non specific hybridization and non specific binding (col. 12, lines 43-43) in nucleic acid hybridization, increase accuracy of detection in nucleic acid hybridization assays (col. 2, lines 43-44), allow more precise control over hybridization (col. 3, lines 28-29), due to an expanded “alphabet” of bases, as well as teaching the use of such with hybridization on supports (col 15, lines 32-33).

The response further asserts that Chee abounds in embodiments of how to expand the “set” of decoding molecules but does not teach or suggest the use of orthogonal nucleobases in coding or decoding oligonucleotides. The response then asserts that Collins describes the use of orthogonal nucleobases to reduce non specific binding and non specific hybridization but does not teach or suggest the use of such bases in a method of identifying a coded test unit as in claim 1. These arguments have been thoroughly reviewed but were not found persuasive. The response appears to argue that since neither reference anticipates the claimed invention, that the invention is not obvious. This amounts piecemeal analysis of specific embodiments of the claims, arguing that they are absent in a single reference, and ignores the teachings of the references as a whole. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Further, as stated in the MPEP 2144: “*The rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law.*” At the time the invention was made, a number of different ways were known to

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optimize specificity, including length of nucleic acid probes, GC content, salt concentration, temperature, and as exemplified and taught by Collins, the use of orthogonal nucleobases.

Collins teaches and provides ample motivation for the use of orthogonal nucleobases in methods requiring the use of nucleic acid hybridization, including in assays requiring hybridization between nucleic acids on solid supports (col. 15, lines 30-35) as noted above and in previous office actions. Further, Chee teaches that orthogonal nucleobases can be used in nucleic acids of Chee and teaches that DBL-IBL probes of the invention of Chee can be made up of nucleic acids. Chee therefore implies the use of orthogonal nucleobases in nucleic acids of the invention of Chee (which includes the DBL-IBL probes of Chee). Coupled with the motivation taught by Collins for using orthogonal nucleobases, the instantly claimed invention is obvious over the teachings of Chee and Collins. For these reasons and the reasons already made of record, the rejection is maintained.

2. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.



Jehanne Sitton

Primary Examiner

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8/10/06